Neural tube defects

An example of multifactorial disorders

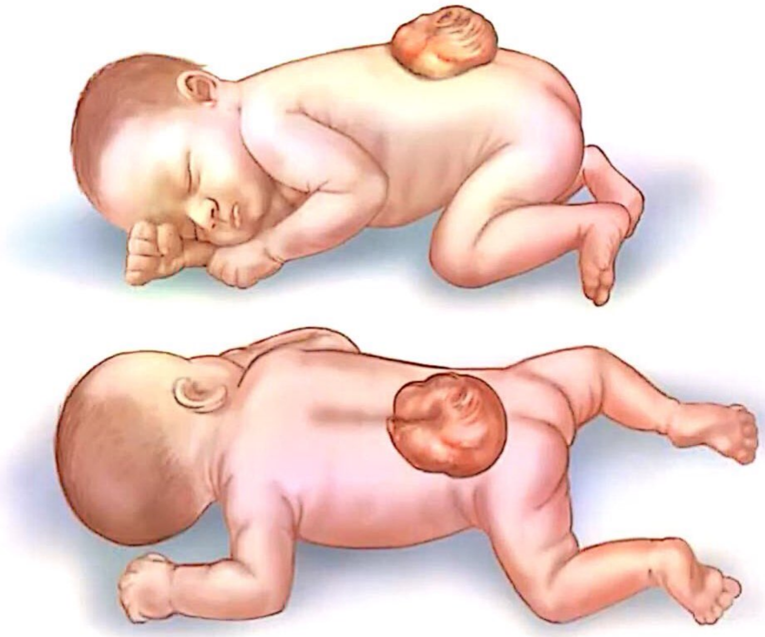
Contents

1. **What is NTDs?**
2. **When and How it is formed?**
3. **Potential cause(s) of NTDs**
4. **Clinical Types of NTDs**
5. **Clinical Manifestations**
6. **Associated malformations**
7. **Management**
8. **Calculation of recurrence risk**
9. **Prenatal diagnosis**
10. **Prevention**

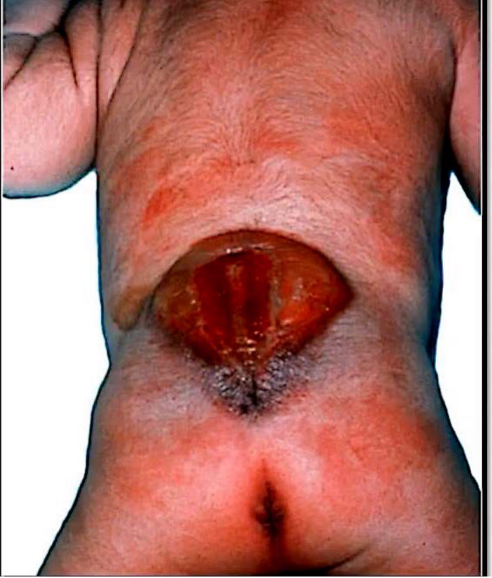
Objectives

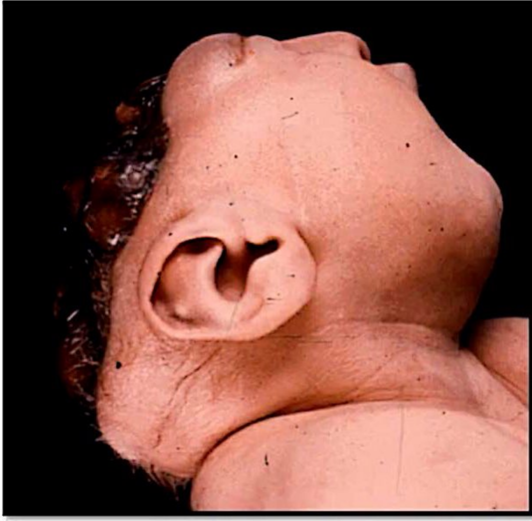
By the end of this session, you are expected to:

1. Define NTDs
2. Describe the mechanism(s) of its formation
3. List the potential causes of NTDs
4. Discriminate different clinical types of NTDs
5. Describe the basic clinical features and their consequences
6. List the probable associated malformations
7. Describe the steps of its management
8. Calculate the recurrence risk of MFI-disorders
9. List the prenatal diagnostic methods
10. Describe the available preventive measures



Neural tube defect in a child





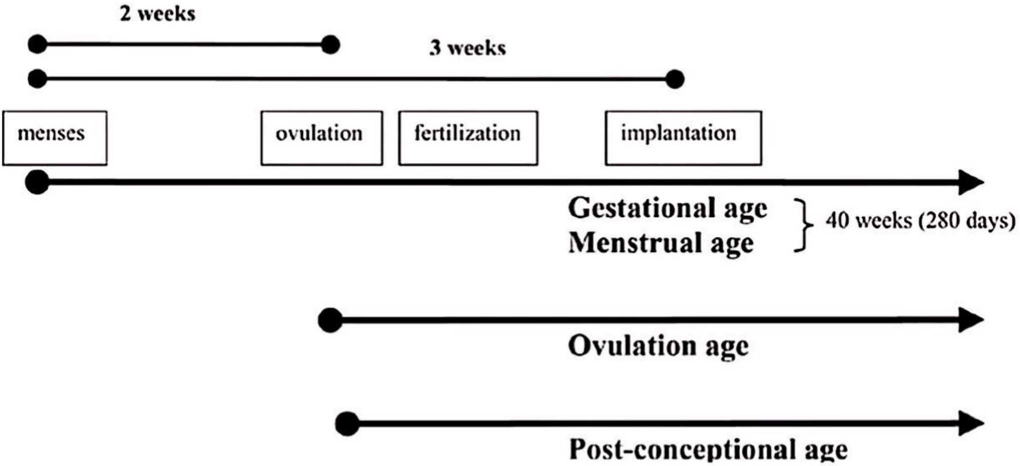
- NTDs are among the most common birth defects resulting in infant death and serious disability, affecting over 300,000 births globally each year.

- NTDs are a spectrum of defects, some are major ones, caused by abnormal development of the neural tube, the structure that is present during embryonic life that gives rise to the central nervous system.

- **Failure of complete fusion (closure) of the neural tube very early in human development gives rise to NTDs.**

- **According to the location and severity of the defect, different types of NTDs are described.**

Pregnancy Timeline



2 weeks

3 weeks

menses

ovulation

fertilization

implantation

Gestational age

Menstrual age

40 weeks (280 days)

Ovulation age

Post-conceptional age

Source: Cunningham FG, Leveno KL, Bloom SL, Hauth JC, Gilstrap LC, Wenstrom KD:
Williams Obstetrics, 22nd Edition: http://www.accessmedicine.com

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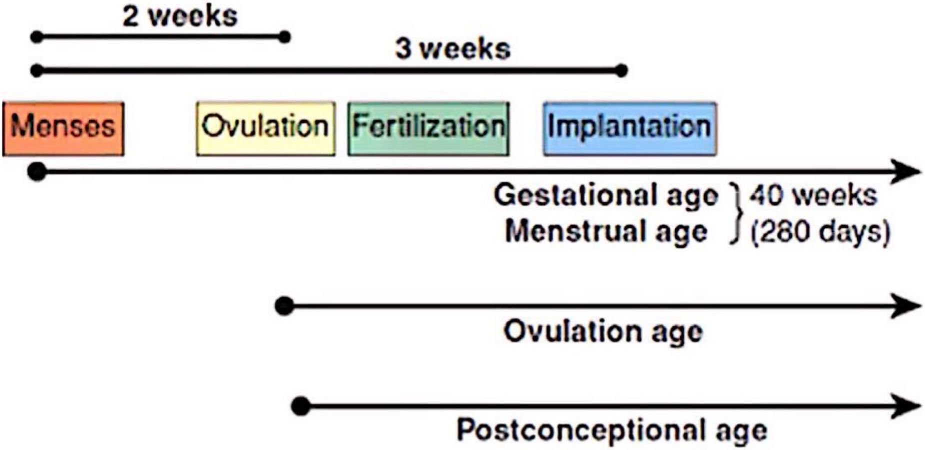
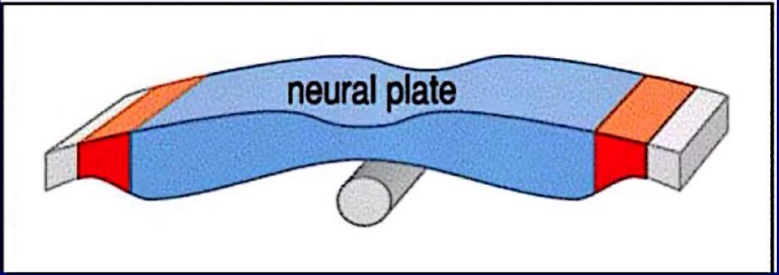

2 weeks
3 weeks
Menses
Ovulation
Fertilization
Implantation
Gestational age
Menstrual age
40 weeks
(280 days)
Ovulation age
Postconceptional age

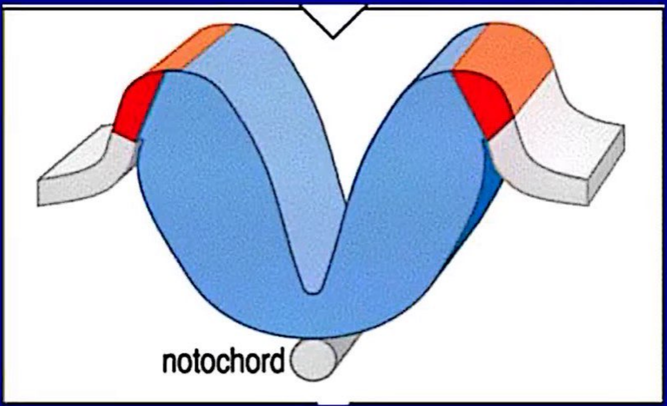
Normal Development

- Nervous system development begins in third week of pregnancy
- Neural plate appears



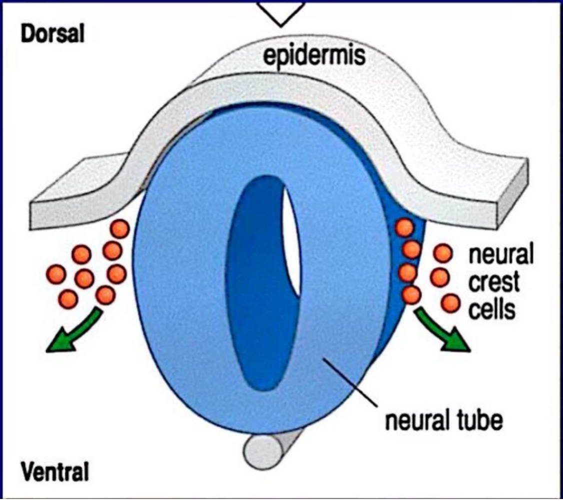
Normal Development

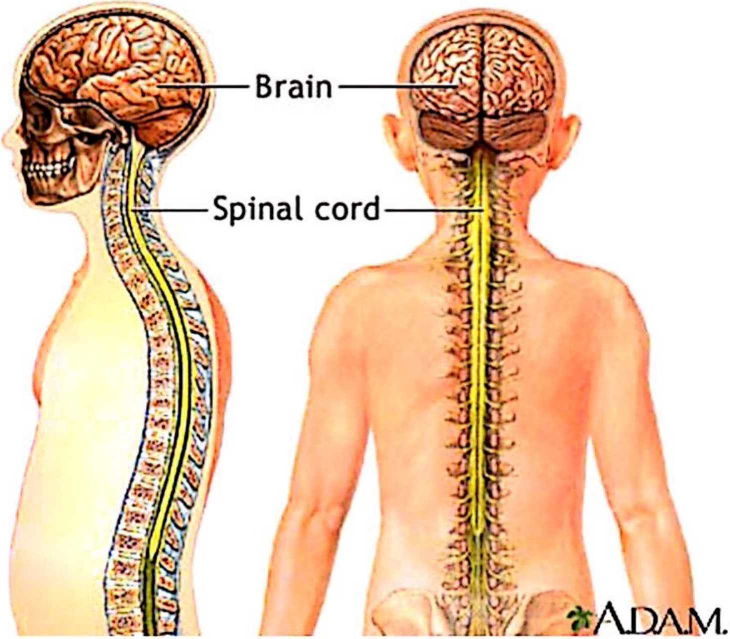
- Edges of neural plate elevate to form neural folds

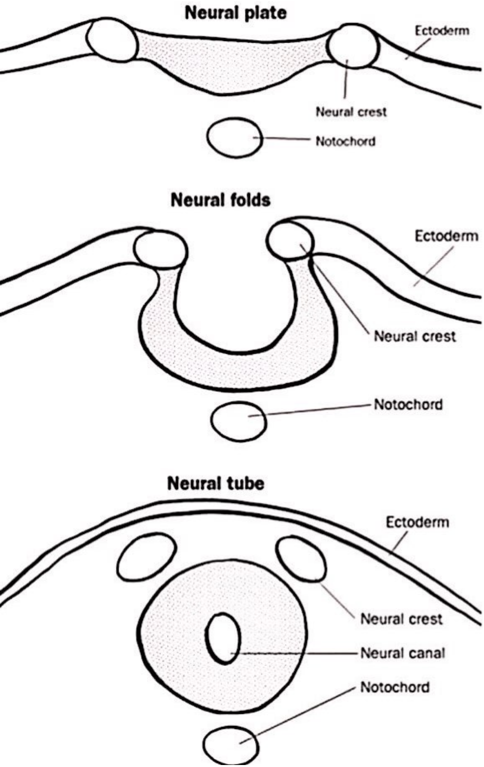


Normal Development

- Neural folds continue to raise and eventually join to create the neural tube




Brain
Spinal cord
A.D.A.M.



Neural Tube Development by dates

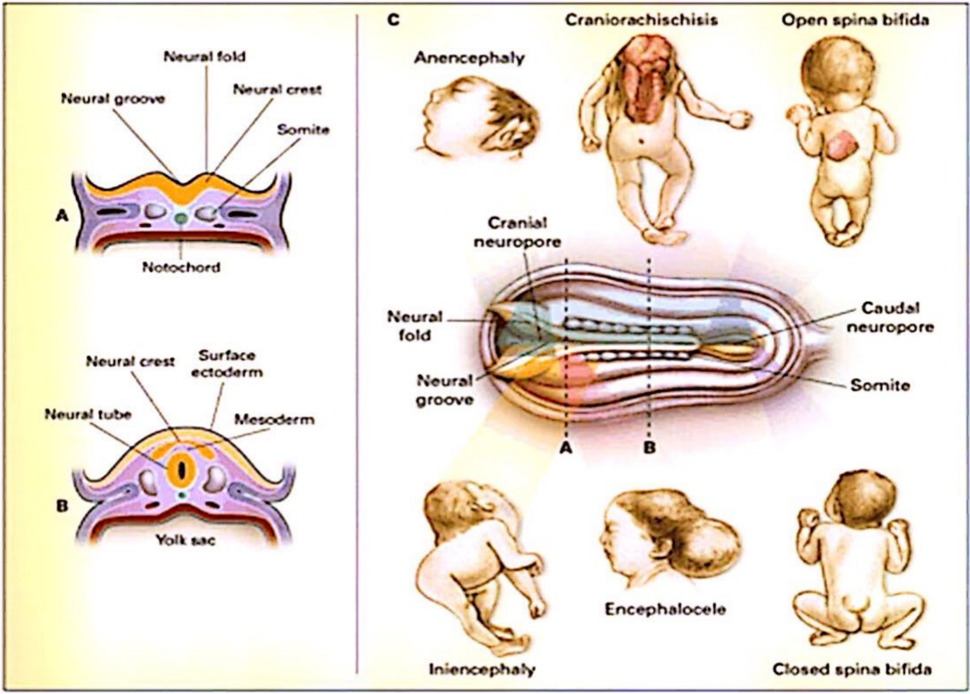
Normal Embryological Development

⇒ Neural plate development -18th day

⇒ Cranial closure 24th day (upper spine)

⇒ Caudal closure 26th day (lower spine)

When do neural tube defects occur?



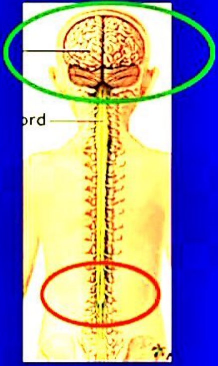
Normal Development

- Neural tube closure is complete by 27-28 days
- This is so early, many pregnancies are not recognized at this point!

http://learningobjects.wesleyan.edu/neurulation/animation.php

Neural Tube Defects

- Caused by problems in closing of the neural tube during development
- May affect any part of the brain or spinal cord
- Many different types
  - Spina bifida = most common
  - Anencephaly
  - Many other variants



What might cause NTDs?

Being a multifactorial disorder, NTDs result from the combined effects of genetic and environmental factors.

There is no one cause of NTDs, but we have many RISK FACTORS.

- Genetic factors
- Environmental factors (Teratogens)

What factors contribute to neural tube defects?

- **Genetic factors → polygenic**
  - more than one gene of small effect, or multiple genes implicated

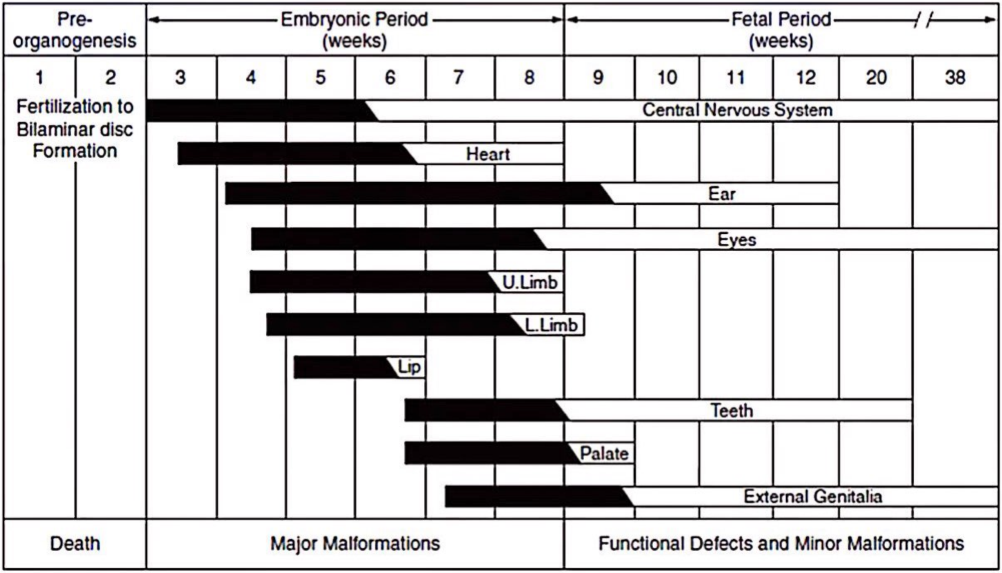
Evidence of genetic factors:

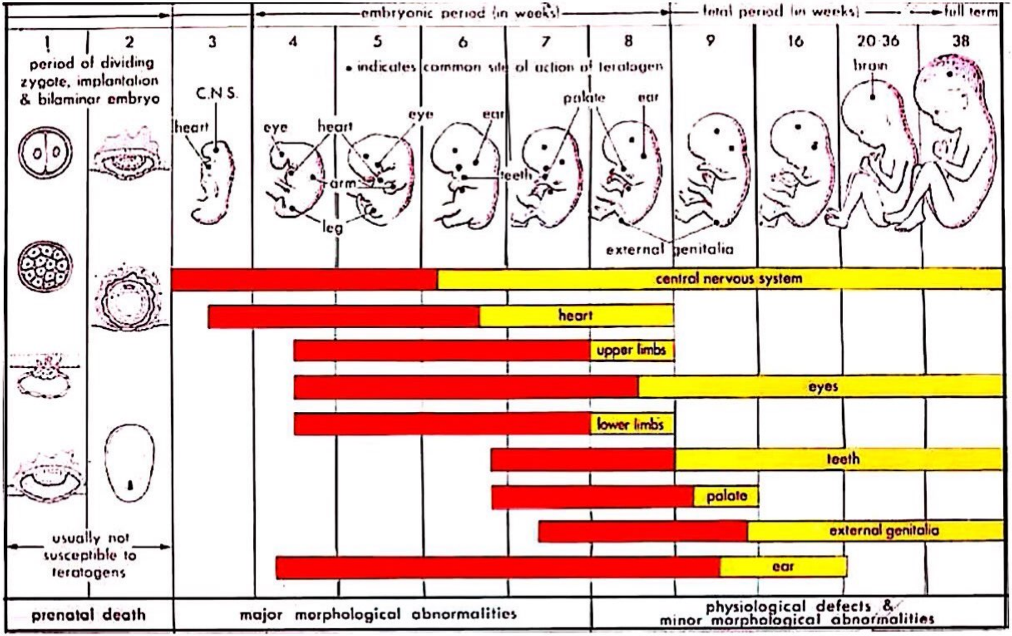
- More common in North America and UK, and less common in Asian countries (geographic distribution) / ethnic groups
- Familial aggregation of NTD cases
- Previous affected pregnancy is a risk factor
- Certain gene mutations are shown to have an effect on incidence of NTD in certain patients (methylene tetrahydrofolate reductase MTHFR-mutations) → folate deficiency

- Teratogens →
- Remember what these are….
  - Maternal nutritional deficiencies notably, folic acid deficiency
  - Maternal obesity
  - Maternal diabetes
  - Excessive heat exposure (hyperthermia)
  - Drugs that affect folic acid metabolism
  - Prior affected pregnancy
  - Maternal smoking
  - Others

90% of women have NO risk factor!!!

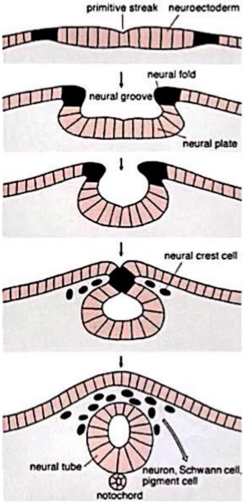
Susceptibility to teratogenesis for different organ systems. Solid bar indicates highly sensitive periods.

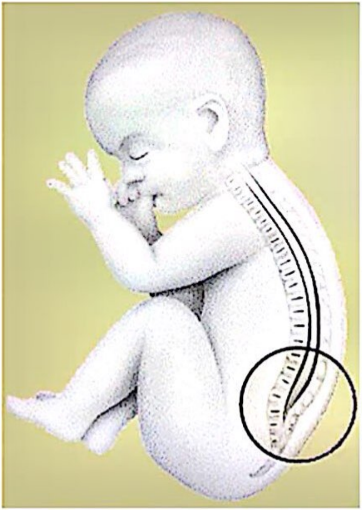




Taken from Moore & Persaud 'Before we are Born'

Neural Tube Defects





Is there more than one clinical type of NTD?

If yes, what are they?

Classification of NTDs

1. Open vs. closed

Depending on whether the covering skin is intact or not

2. Site:

Cranial vs. caudal i.e. brain vs. spine

- Anencephaly (1/3)
- Spina bifida (2/3)

3. Location:

Upper vs. lower

- Upper → anencephaly, cervical and thoracic defects
- Lower → lumbar and sacral defects

Brain:

- Anencephaly
- Encephalocele

Spinal cord:

- Spina bifida occulta
- Spina bifida cystica
    - Meningocele
    - Myelomeningocele
    - Lipomeningocele

Other types

- Hydranencephaly
- Iniencephaly
- Craniorachischisis

Upper vs. lower defects:

Upper defects:

- Tend to be associated with other congenital malformations
- Have a significant risk of recurrence
- Occur at a greater frequency in females

Lower defects:

- Are more often isolated
- Have lower occurrence risk
- Have unbiased or slight male preponderance

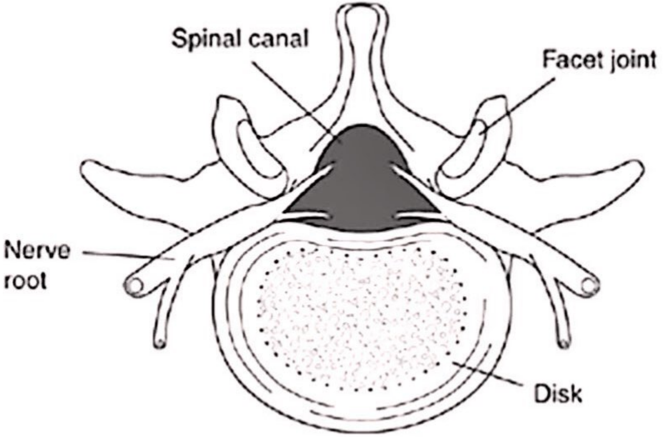
Earlier:

Upper defects result from failure of primary neurulation, while lower defects from disturbance in secondary neurulation

More recent studies suggest:

Transition zone between primary and secondary neurulation occurs at midsacral level suggesting that the great majority of both upper and lower defects occur within the region formed by primary neurulation.

Normal



Normal Vertebra (Cross Section)

What is Spina Bifida?

A midline defect of the:

⇒ bone,

⇒ skin,

⇒ spinal column, &/or

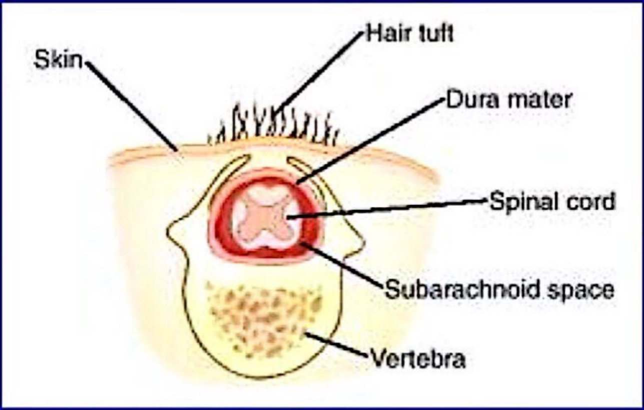
⇒ spinal cord.

Spina bifida occulta

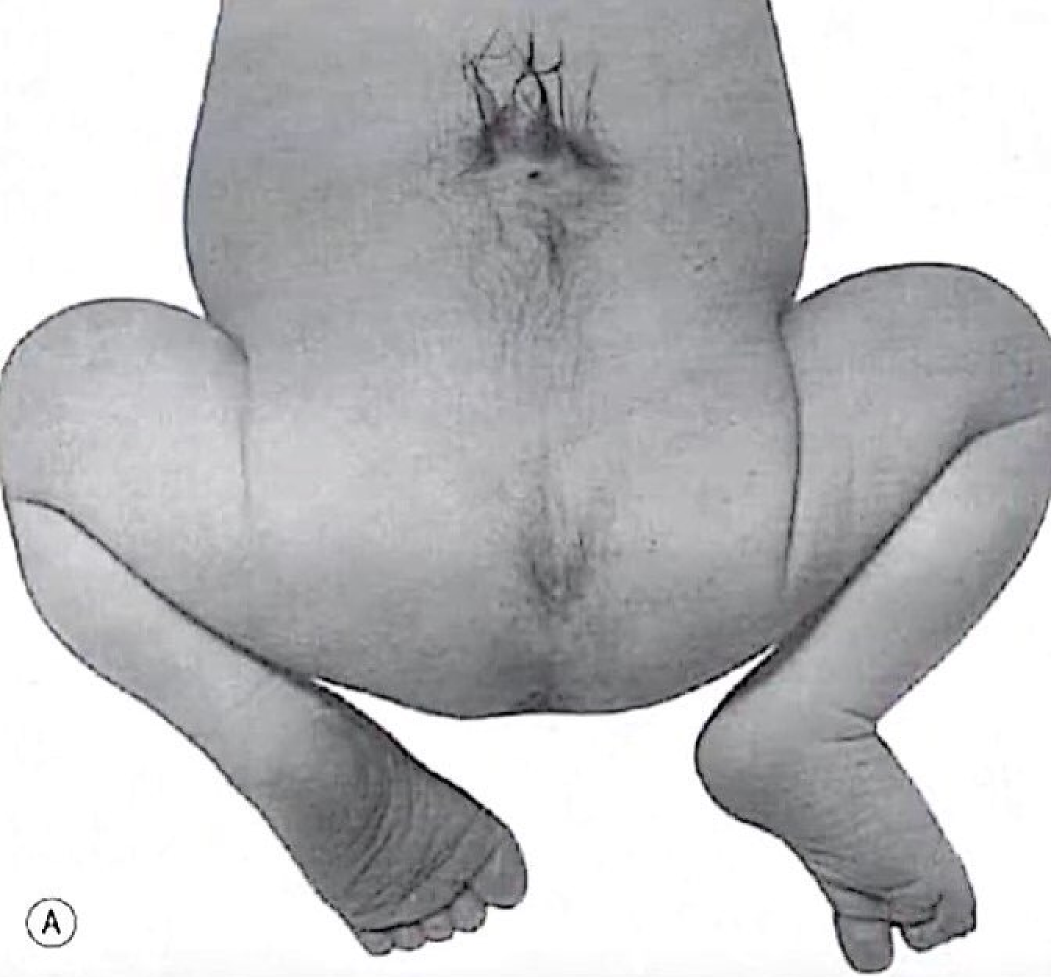
(*occulta* = closed)

A condition involving non-fusion of the halves of the vertebral arches without disturbance of the underlying neural tissue

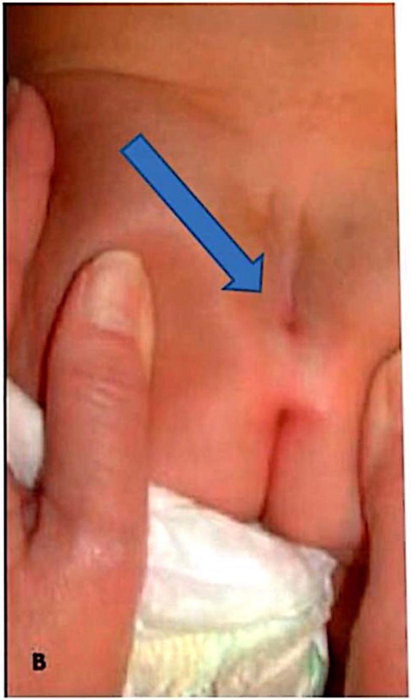
Spina bifida occulta

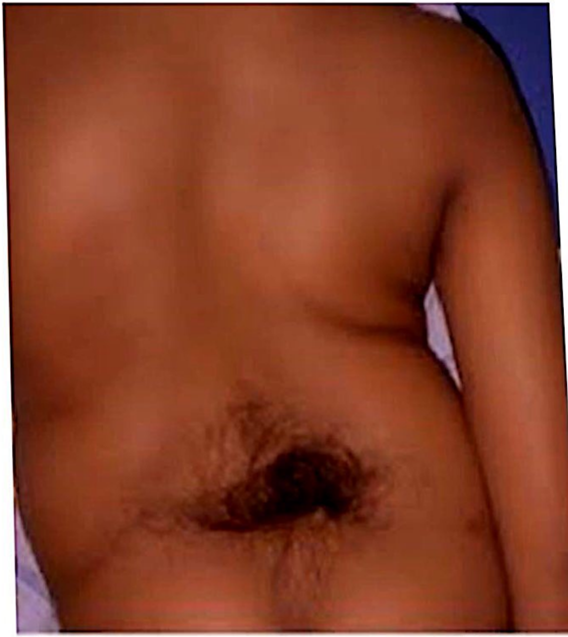


- Cannot be detected by screening
- Patients do not have symptoms
- Does not require treatment



Oligny & Siebert: Potter's Pathology of the Fetus, Infant and C

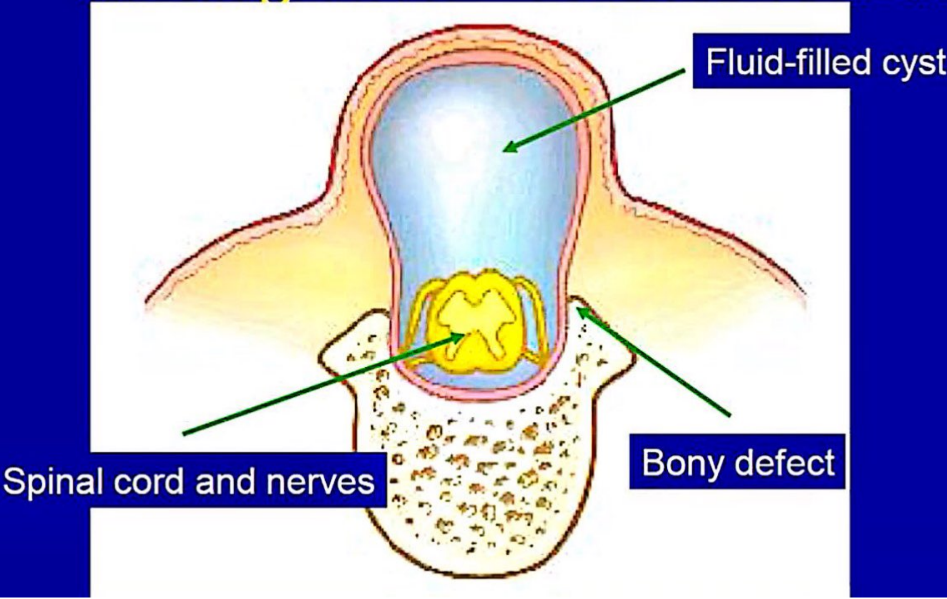

B



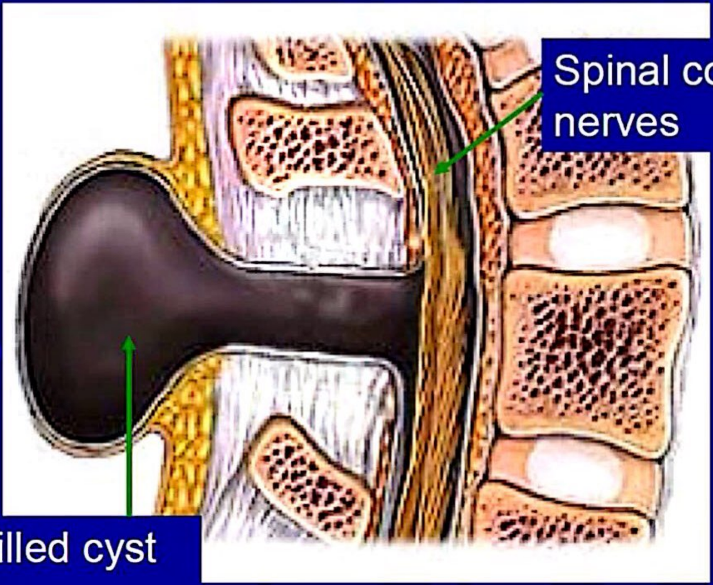
Spina bifida cystica / aperta

- Meningocele
- Myelomeningocele = Spina Bifida
- Lipomeningocele
- Others

Meningocele – Cross Section

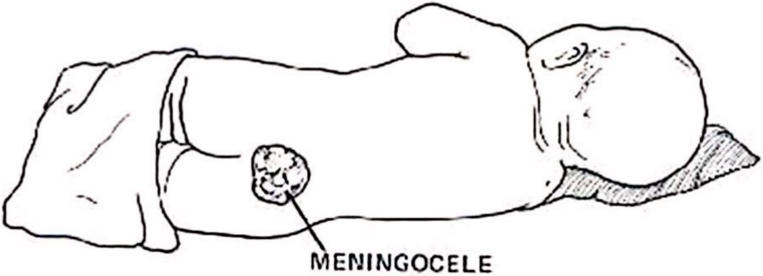


Meningocele- Side View



Spinal cord and nerves

Fluid-filled cyst



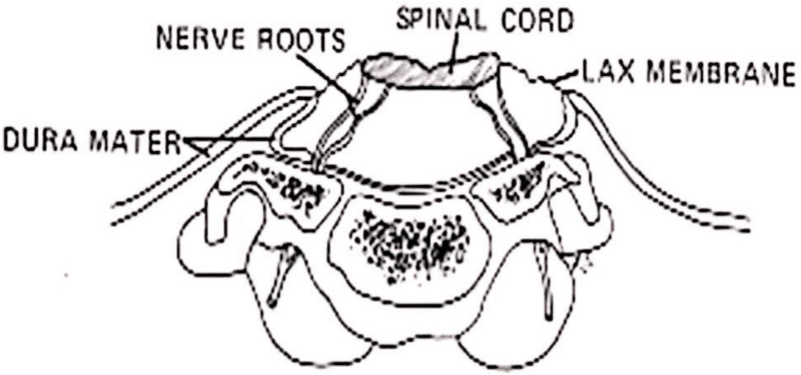
Meningocele (*cele* = sac)

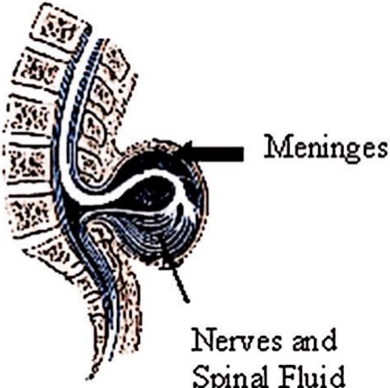
Fluid-filled sac with meninges involved but neural tissue unaffected

Cyst must be surgically removed (Why?)

Patients usually have normal development

The spinal defect with myelomeningocele

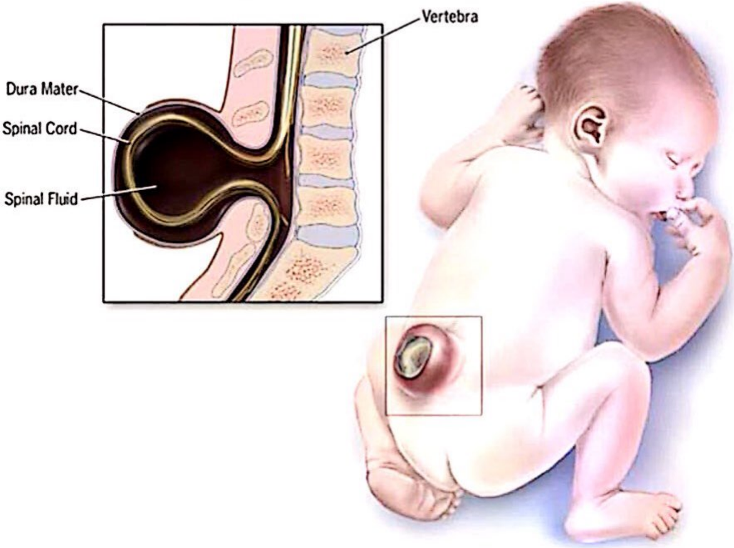




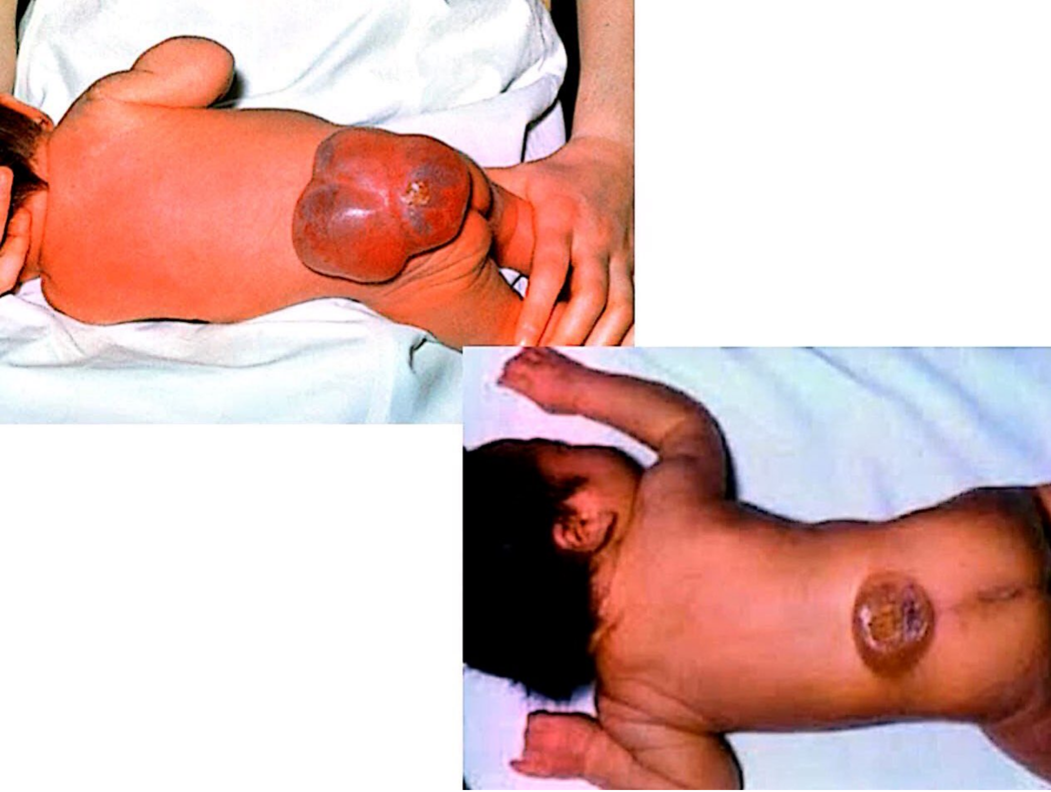
Myelomeningocele

or *spina bifida*:
meninges and spinal tissue protruding through a dorsal defect in the vertebrae

Meningomyelocele



Spina Bifida (Open Defect)



Meningomyelocele

Must be closed surgically:

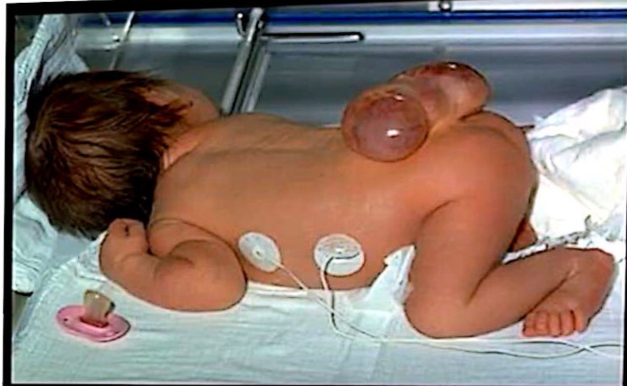
- Thin cover = high infection risk if not treated
- Patients often have leg paralysis or bowel/ bladder control problems
- Seizure disorders, kidney problems could also be seen

Lipomeningocele

(*lipo* = fat)

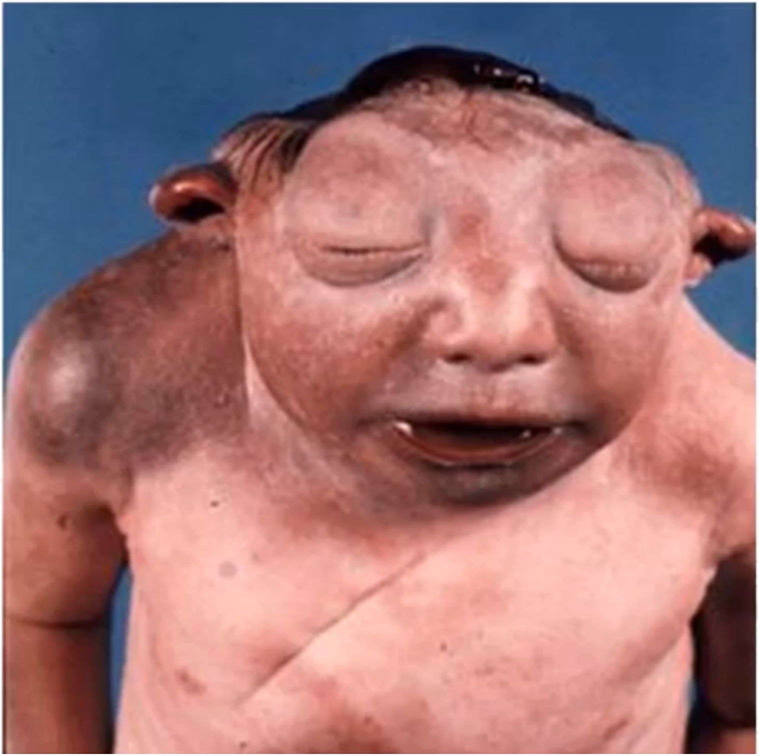
lipoma or fatty tumor located over the lumbosacral spine.

Associated with bowel & bladder dysfunction

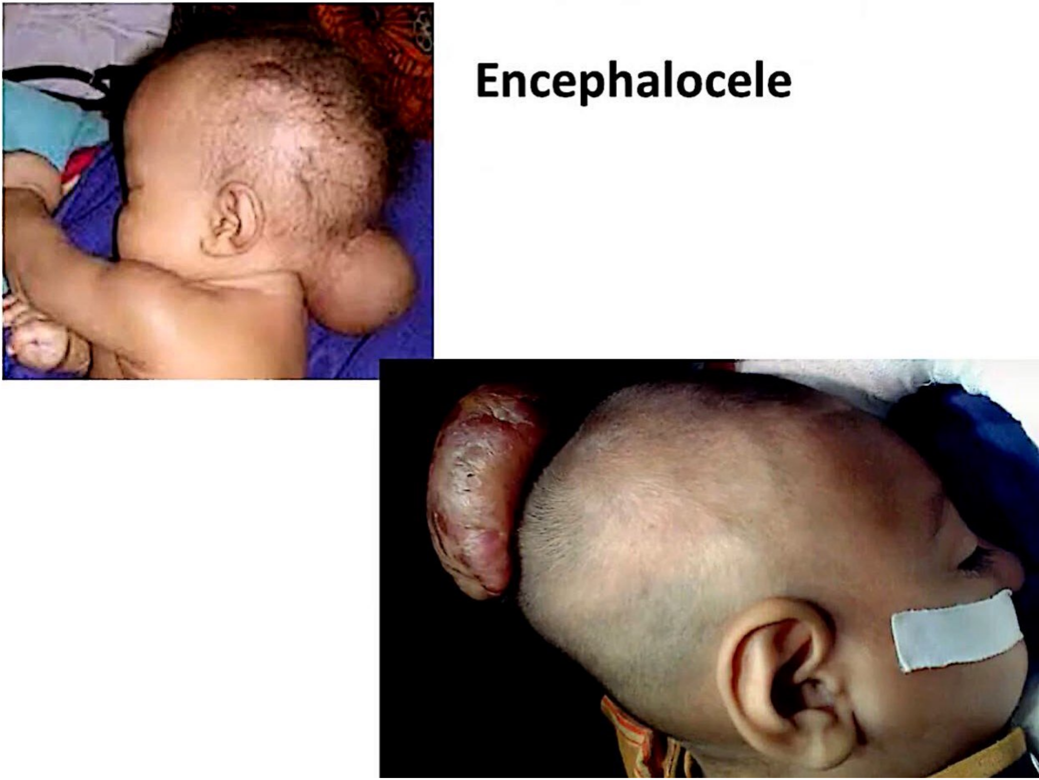


Anencephaly

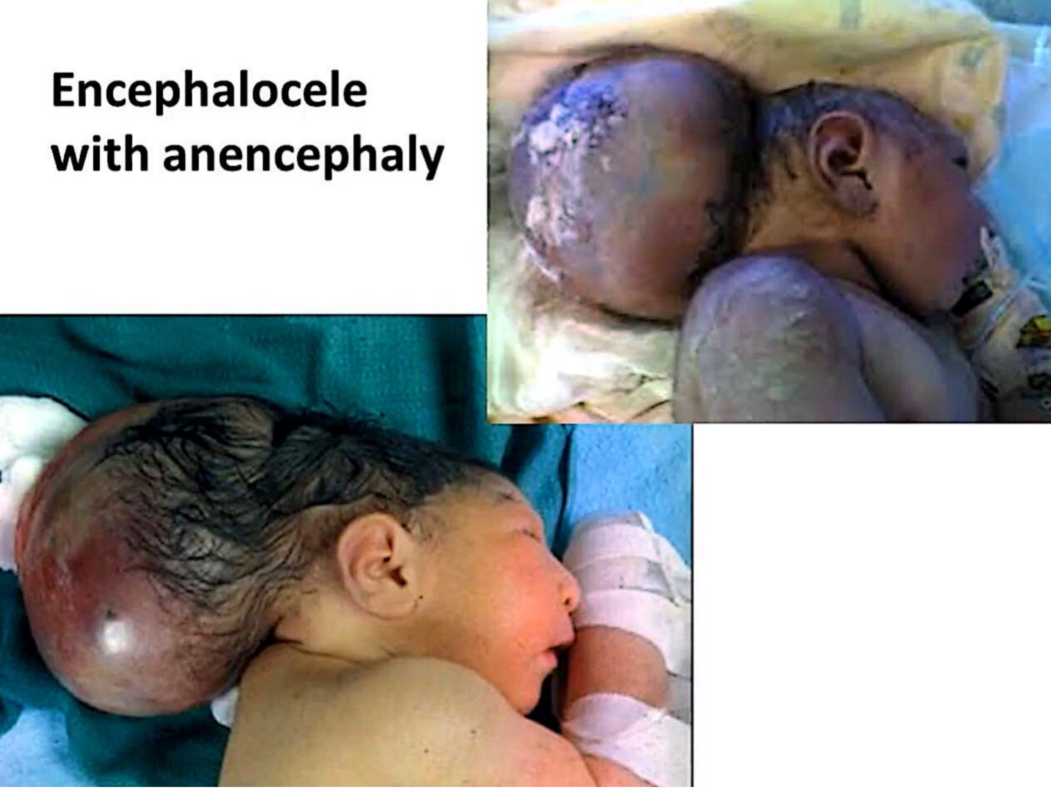
- Severe problem with brain and skull development
- Top part of head and brain does not form
- Patients are blind, deaf, unconscious
- Patients do not usually survive longer than few days

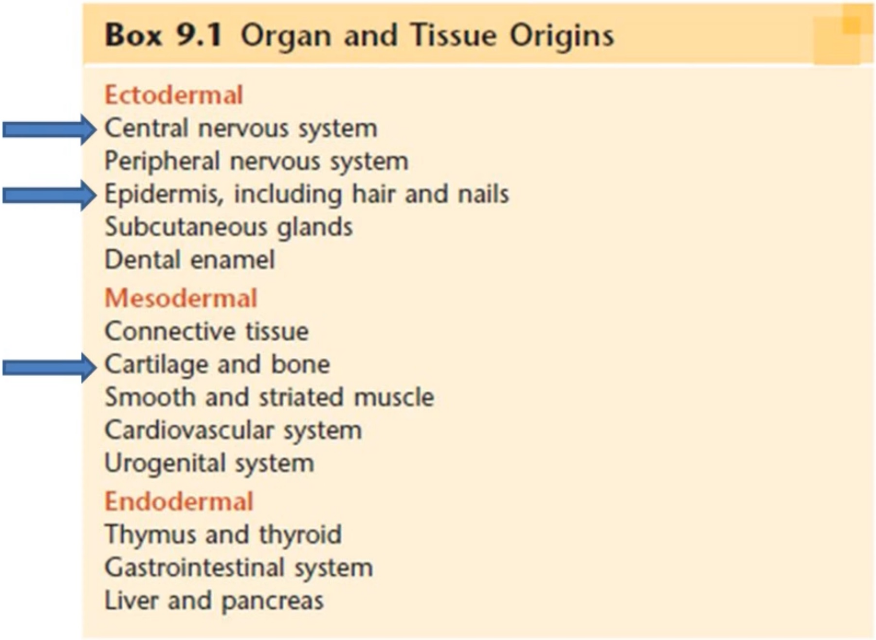


Encephalocele



Encephalocele with anencephaly





Box 9.1 Organ and Tissue Origins

Ectodermal

Central nervous system
Peripheral nervous system
Epidermis, including hair and nails
Subcutaneous glands
Dental enamel

Mesodermal

Connective tissue
Cartilage and bone
Smooth and striated muscle
Cardiovascular system
Urogenital system

Endodermal

Thymus and thyroid
Gastrointestinal system
Liver and pancreas

Is there any associated anomaly?

1. Defects are visible at birth (except occulta type).
2. Consequences of brain / nervous tissue involvement:
    - Lower limb paralysis and deformities e.g. club foot
    - Bladder / bowel control dysfunction
    - Seizures
    - Motor dysfunction (movement)
    - Sensory involvement
    - Intellectual / learning disability
    - Others
3. Associated hidden anomalies

Associated anomalies:

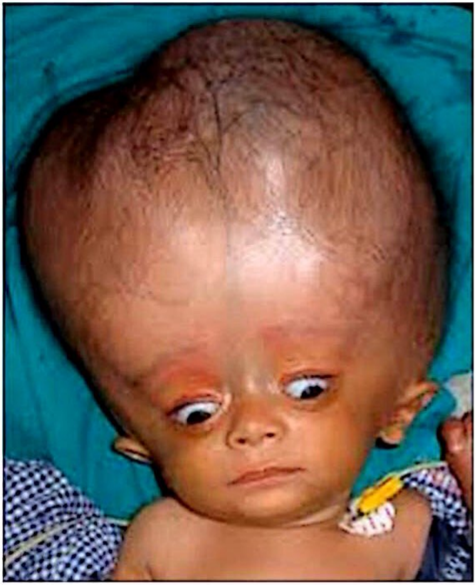
- Hydrocephaly (water in the brain ??!!)
- Arnold Chiari malformation and its associated problems

Complications:

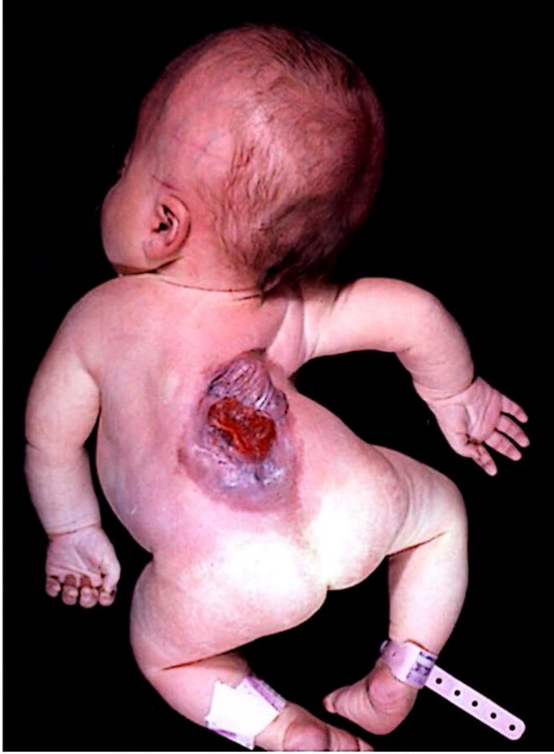
* Skin breakdown

* Bed sores (Ulcers) for bed-ridden patients

Hydrocephaly



Sun setting sign



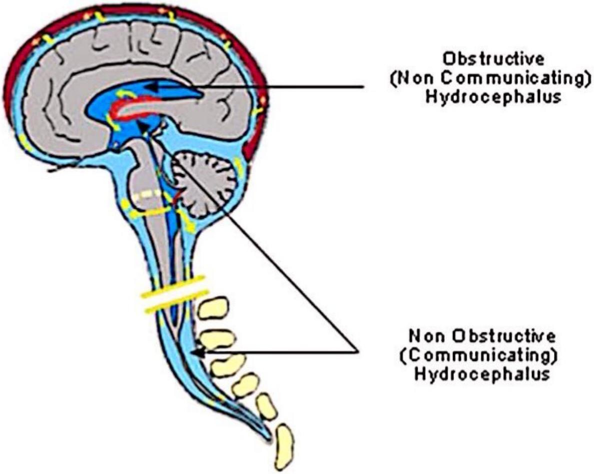
Hydrocephaly & MMC

Hydrocephalus

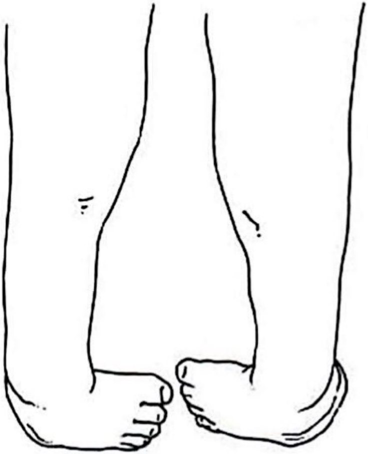
Anatomical changes associated with a cervical lesion:

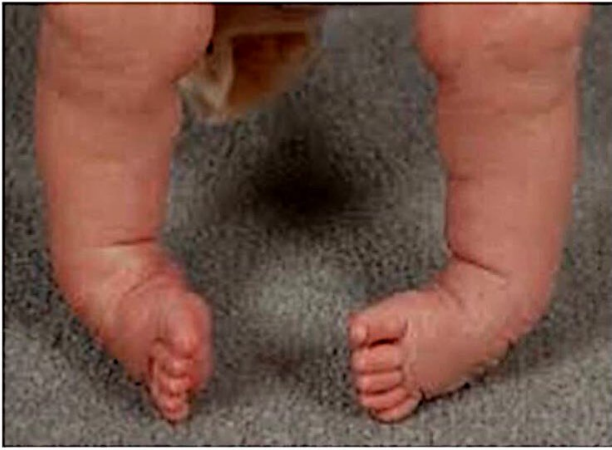
An enlarged head caused by *hydrocephalus*

(excessive CSF accumulation in ventricular system)



Structural Problems: Club Foot





How can you manage such cases?

Management:

1. Diagnosis is evident at birth.
2. Most cases have no evident risk or a treatable cause.
3. NTDs are static non-progressive conditions; any progress is due to consequences of the defects.
4. Treatment is directed towards:
    a. Surgical correction of all defects.
    b. Rehabilitation and physical therapy.
    c. Prevention of complications.

What is the prenatal diagnostic method(s) used in NTDs?

Ultrasonography

For locating back lesion vs. cranial signs

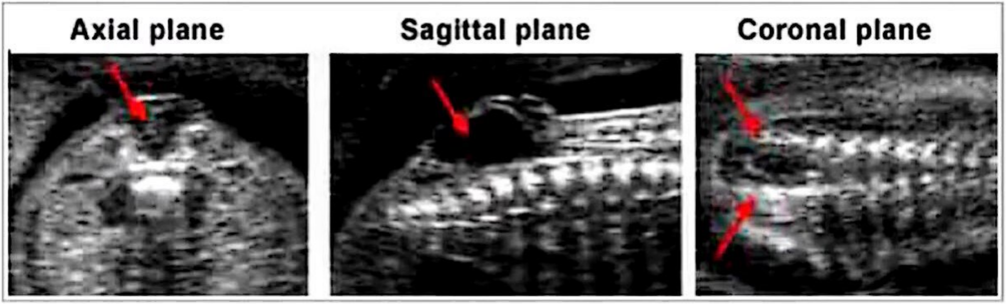
Banana sign and lemon sign

→ If it came positive:

Detection of alpha-fetoprotein

- Amniocentesis (AFAFP)
- Amniotic fluid acetylcholinesterase (AFAChE) level
- Maternal serum (MSAFP) **(16-18 weeks)**

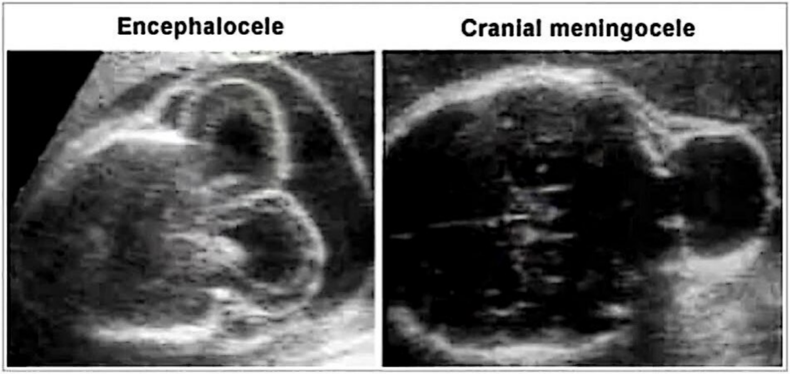
(Unconjugated estriol and HCG) → both normal



Axial plane

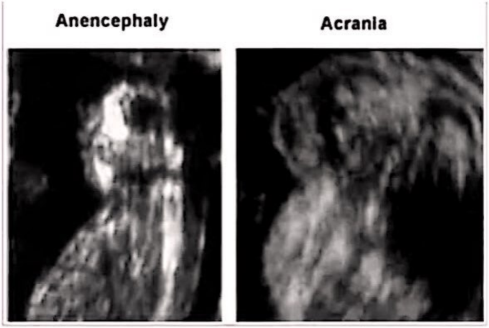
Sagittal plane

Coronal plane



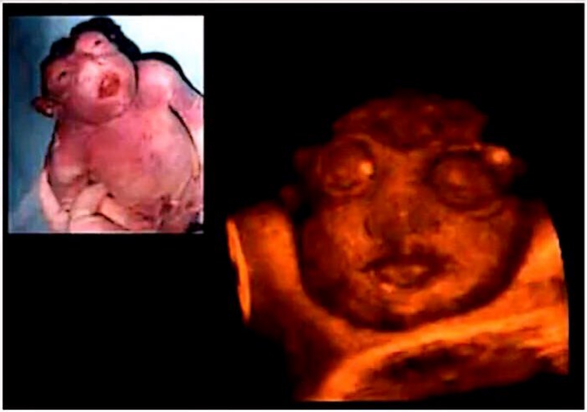
Encephalocele

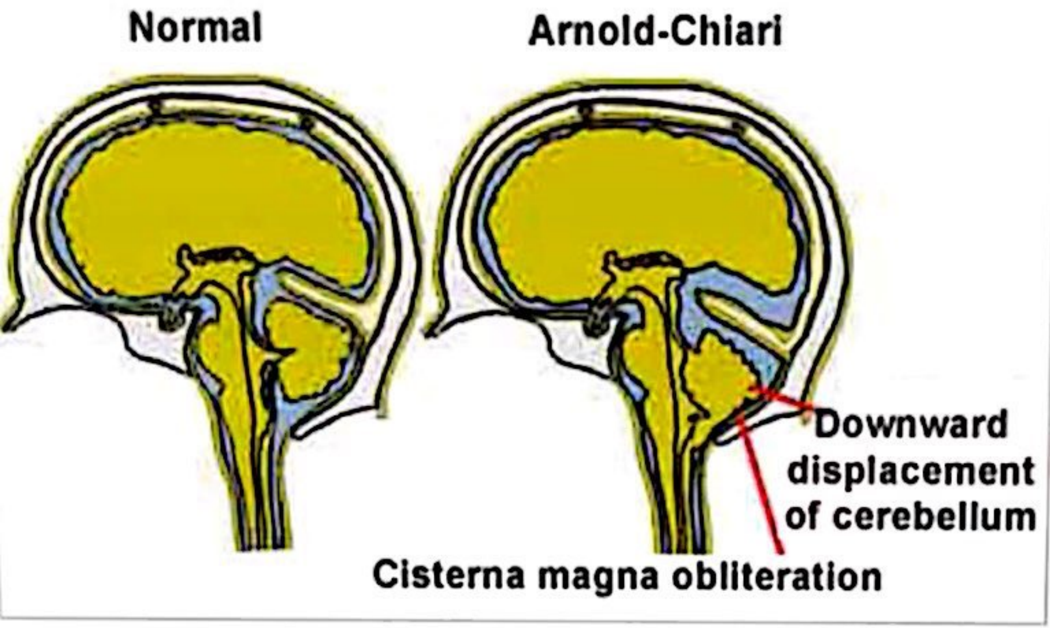
Cranial meningocele

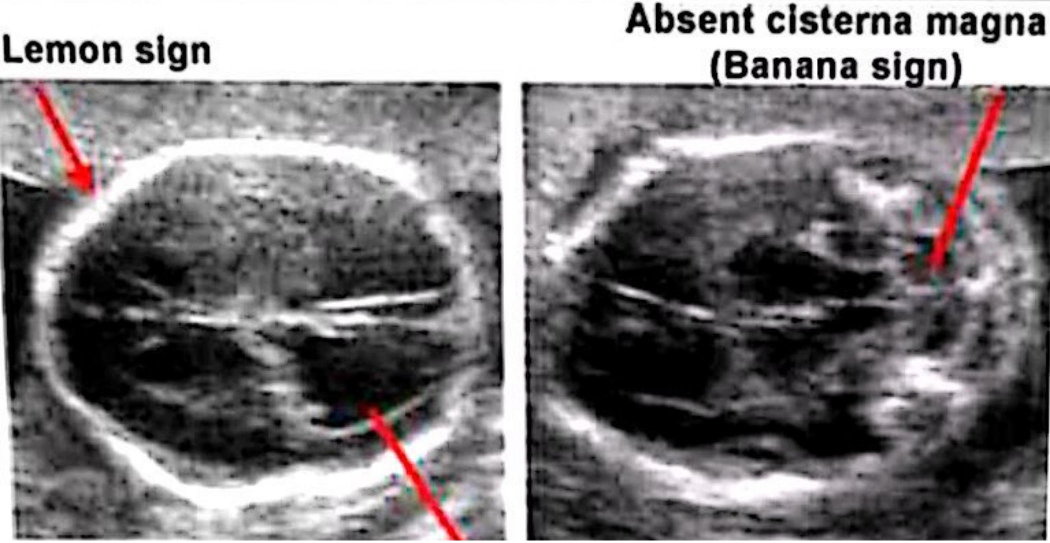


Anencephaly

Acrania




Normal
Arnold-Chiari
Downward displacement of cerebellum
Cisterna magna obliteration


Lemon sign
Absent cisterna magna (Banana sign)

CONDITION	**MSAFP**	**UE3**	**HCG**
Neural tube defects	Increased	Normal	Normal
Trisomy 21	Low	Low	Increased

How to calculate the recurrence risk in Multifactorial disorders?

In general,

1. MF-disorders usually occur in 1-5% in any community.
2. Higher percentage is given to a family with a previously affected family member
3. Recurrence is higher if the severity is more (anencephaly and MMC > spina bifida occulta)
4. More affected family members → ↑ recurrence
5. If the two sexes have a different probability of being affected, the least likely sex, *if affected*, is the most likely sex to produce an affected offspring (e.g. pyloric stenosis; M:F ratio is 7:1)

How can you prevent NTDs?

What can we do with abnormal genes?

CRISPR (clustered regularly interspaced palindromic repeats), are powerful tools for genome editing

How can we modify the potential risk factors?

In 1996, the United States Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flour and other grain products.

It is important to note that during the first 4 weeks of pregnancy (when most women do not even realize that they are pregnant), adequate folate intake is essential for proper operation of the neurulation process.

Therefore, women who could become pregnant are advised to eat foods fortified with folic acid or take supplements in addition to eating folate-rich foods to reduce the risks of serious birth defects.

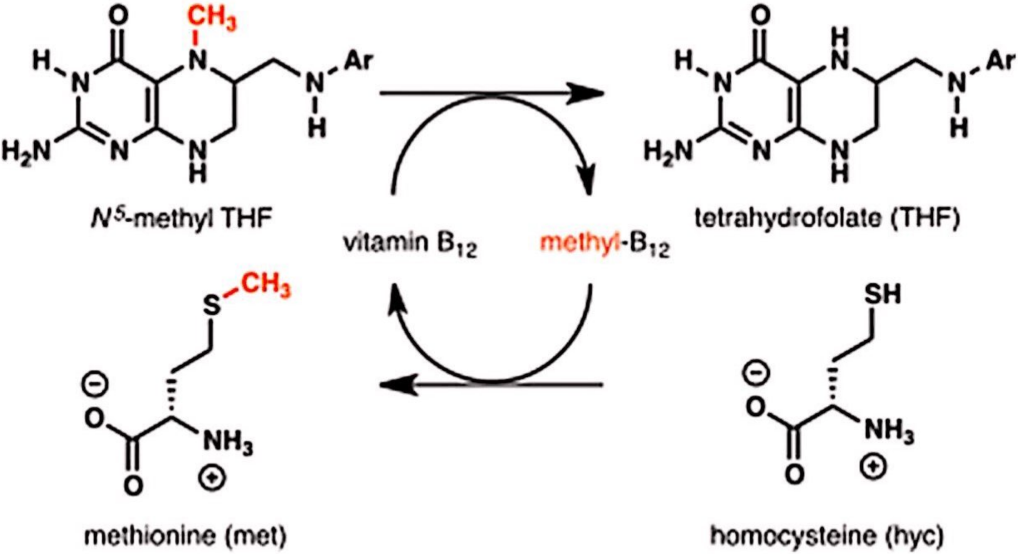
Foods naturally high in folates include

Leafy greens (broccoli, spinach)
Legumes
Liver

In Canada, mandatory fortification of selected foods with folic acid has been shown to reduce the incidence of NTDs by 46%.

"**All women of childbearing age in the United States who are capable of becoming pregnant** should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other neural tube defects."

- Folic acid is a "B" vitamin that can be found in such foods as: **cereals, broccoli, spinach, corn and others**, and also as a vitamin supplement.


N^5-methyl THF
tetrahydrofolate (THF)
vitamin B_{12}
methyl-B_{12}
methionine (met)
homocysteine (hyc)

Consumption of folate (0.4 mg/day) should start 3 months before pregnancy and all the way through pregnancy.

Higher doses may be required (1-5 mg/day)

Intake does not rule out the need for screening

- There is definitely an association between folic acid supplementation and decreased rates of NTDs

- ***Folic acid (a monoglutamic acid) is the*** **oxidized and most active form of the vitamin; found rarely in food, it is the form used in vitamin preparations and food fortification.**

- **The distinction between food folate and folic acid is important because of differing bioavailability (i.e. food folate is only about half as available as folic acid consumed on an empty stomach).**

Is it reduced folate intake or a metabolic defect in folate metabolism that is more likely to increase the risk for NTDS and other birth defects?

- **Folate** (vitamin B_9) and **vitamin B_{12}** are very important in reducing the occurrences of NTDs.

- Folate is required for the production and maintenance of new cells, for DNA synthesis and RNA synthesis. Folate is needed to carry one carbon groups for methylation and nucleic acid synthesis.

- Early human embryo may be particularly vulnerable to folate deficiency due to differences of the functional enzymes in this pathway during embryogenesis combined with high demand for post translational methylations of the cytoskeleton in neural cells during neural tube closure.

What is the role of folate (folic acid) in normal states?

How can folate reduces the incidence of or prevent NTDs?

- **Failure of post-translational methylation of the cytoskeleton, required for differentiation has been implicated in neural tube defects.**
- **B_{12} is an important receptor in folate biopathway → B_{12} deficiency contributes to risk of NTDs as well.**

- **Importantly, a deficiency of folate itself does not cause NTDs BUT folate supplementation overcomes a metabolic block.**

- **The association seen between reduced neural tube defects and folic acid supplementation is due to a gene-environment interaction such as vulnerability caused by the C677T (MTHFR) variant.**

- **Supplementing folic acid during pregnancy reduces the prevalence of NTDs by not exposing the otherwise subclinical mutation to aggravating conditions.**

- **There is substantial evidence that direct folic supplementation increases blood serum levels of bioavailable folate → activity of dihydrofolate reductase in human liver.**

- *Folate is a generic term for a water-soluble, B-complex vitamin*
- *It* serves as an essential coenzyme in single-carbon transfers in the metabolism of nucleic and amino acids
- fills an important function in purine and pyrimidine metabolism.
- It occurs in certain natural foods as polyglutamate, a form less absorbed than free folate.

- **A diet rich in natural folate (350 µg/d) can show as much increase in plasma folate as taking low levels of folic acid (250 µg/d) in individuals.**

- **Only general food fortification with folic acid reduces neural tube defects.**

What are folates?

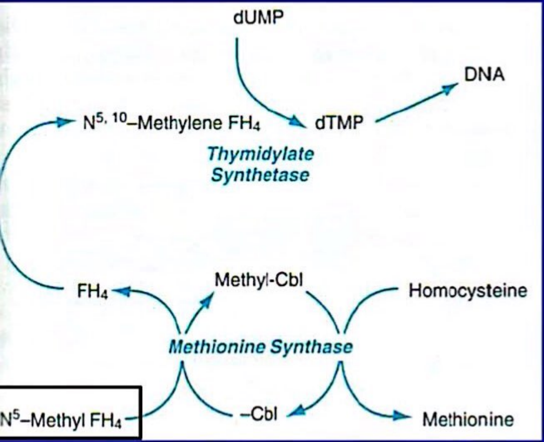


Figure 13-21, Robbins and Cotran Pathologic Basis of Disease, 7th ed. p. 641

- Folates important for
  - – Amino acids
    - Methionine synthesis
    - Histidine metabolism
    - Serine-glycine metabolism
  - – DNA
    - Thymidylate synthesis
    - Purine synthesis

THANK YOU